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TITLE: The Role of NF-kappaB in Promotion and Survival of Androgen-Dependent and Independent Prostate Cancer

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13. ABSTRACT (Maximum 200 Words)

Androgen ablation remains the only effective form of systemic therapy for patients with advanced prostate cancer due to the ineffectiveness of standard forms of cancer therapy. The transcription factor NF-kappaB has emerged as a key regulator of oncogenesis based on its ability to promote cell proliferation, suppress apoptosis, and to promote metastasis and angiogenesis. Additionally, NF-kappaB has been shown to be activated by cancer therapies such as radiation and chemotherapy to suppress therapy-induced apoptosis. The underlying hypothesis of this proposal is that constitutive activity of NF-kappaB in androgen-dependent prostate cancer provideds either a growth or survival function and that enhanced activation of NF-kappaB, potentially through p65/RelA phosphorylation, promotes recurrence of the androgen-independent phenotype. It also proposed that NF-kappaB activation provides a strong level of prostate cancer chemoresistance. The aims (modified following funding reduction) were to: (1) characterize therapeutic approaches for the inhibition of androgen-dependent and androgen-independent CWR22 tumor growth and (2) determine whether combination treatment of chemotherapy and NF-kappaB inhibitors will provide a new therapeutic approach for prostate cancer treatment.

14. SUBJECT TERMS
NF-kappaB, prostate cancer therapy, suppression of apoptosis, chemoresistance, androgen receptor function, IKK inhibitors

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INTRODUCTION:

Androgen ablation remains the only effective form of systemic therapy for patients with advanced prostate cancer due to the ineffectiveness of standard forms of cancer therapy. The transcription factor NF-kappaB has emerged as a key regulator of oncogenesis based on its ability to promote cell proliferation, suppress apoptosis, and to promote metastasis and angiogenesis. Additionally, NF-kappaB has been shown to be activated by cancer therapies such as radiation and chemotherapy to suppress therapy-induced apoptosis. The underlying hypothesis of this proposal is that constitutive activity of NF-kappaB in androgen-dependent prostate cancer provides either a growth or survival function and that enhanced activation of NF-kappaB, potentially through p65/RelA phosphorylation, promotes recurrence of the androgen-independent phenotype. It is also proposed that NF-kappaB activation provides a strong level of prostate cancer chemoresistance. The aims (modified following funding reduction) were to: (1) characterize therapeutic approaches for the inhibition of androgen-dependent and androgen-independent CWR22 tumor growth and (2) determine whether combination treatment of chemotherapy and NF-kappaB inhibitors will provide a new therapeutic approach for prostate cancer treatment.

BODY:

Note: Following review of this application, it was recommended that the funding be cut to one-third of the requested amount. As a consequence, the Statement of Work was amended to focus on the therapeutic directions of the proposal. Thus, the new (amended) Statement of Work was to: (1) characterize therapeutic approaches for the inhibition of androgen-dependent and androgen-independent CWR22 tumor growth (fully developing the CWR22 model, developing the TRAMP and PTEN models for the laboratory, test different NF-kappaB inhibitors for inhibition of prostate tumor growth in these models, and determine the mechanism of tumor growth inhibition) and (2) determine whether combination of chemotherapy and NF-kappaB inhibitors will promote prostate cancer regression.

Additional note: Due to funding overlap with a newly awarded National Cancer Institute grant, DAMD17-03-1-0140 was terminated on August 31, 2003 (3 months of total funding).

In the 3 month period, we succeeded in repeating our CWR22 model for prostate tumor growth (although the results were erratic in terms of tumor regression and regrowth). We also obtained the TRAMP model for prostate cancer and made an agreement to obtain the PTEN model for prostate cancer. We have also contacted Millenium Pharmaceuticals about obtaining a new IKK inhibitor (more effective than the one that we had previously tested).

KEY RESEARCH ACCOMPLISHMENTS:

- Testing the CWR22 recurrent, androgen-independent prostate cancer model.
- Obtaining the TRAMP model for prostate cancer from Dr. Greenberg.
- Obtaining permission to receive the PTEN animal model (from Dr. Y. Whang).

REPORTABLE OUTCOMES:

None, due to the short funding period.

CONCLUSIONS:

CWR22 model is an erratic model due, potentially, to the instability of the maintained tumor xenograft. Newer models may be needed to better characterize the transition to androgen-independent tumor growth.

REFERENCES:

None.